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Stereoselective Synthesis and Properties of 1-*O*-Acyl-D-Glucopyranoses

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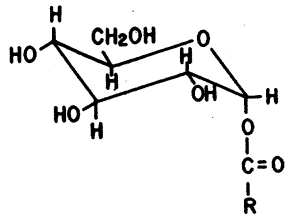
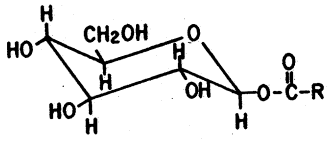
In general, 1-O-acylaldoses, and in particular the derivatives with a cis hydroxyl group at C-2, are difficultly accessible substances. A few 1-O-acyl-D-glucoses have been found in nature, e.g., 1-O-benzoyl-β-D-glucopyranose (periplanetin) in insects (1), stevioside in Stevia Rebaudiana Bertoni (2), asiaticoside from Cantella asiatica (3) and 1-O-galloyl-β-D-glucopyranose in Chinese rhubarb (4). Over the years there have been numerous attempts at preparing anomerically pure

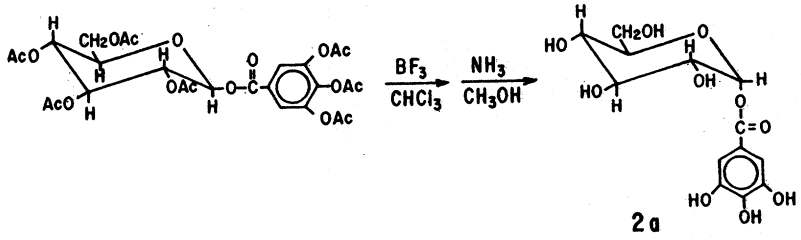


1α



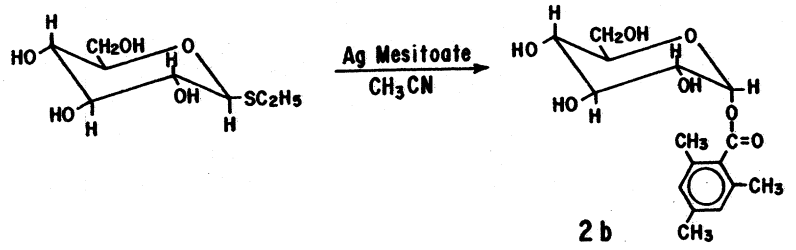
1β

1-α and β-D-glucopyranose esters 1α and 1β using various reactions aimed at controlling the anomerism of the C-1 acylation site. Schmidt (5) prepared the sterically hindered 1-O-galloyl-α-D-glucopyranose 2a in 5% yield through a lengthy five-step synthesis.

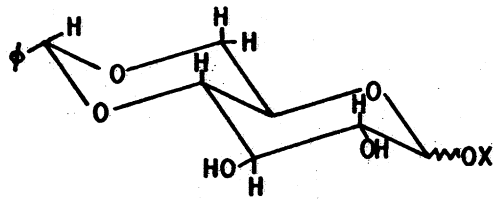


2α

The key steps in this scheme involved a BF_3 isomerization for five days of the more accessible 2,3,4,6-tetra-O-acetyl-1-O-(triacetyl-galloyl)-β-D-glucopyranose followed by preferential deacylation of the more labile acetyl protecting groups. This work represented the first reported preparation of a 1-O-acyl-α-D-glucopyranose 1α. In later studies Fletcher (6) questioned the positional assignment of the ester grouping of Schmidt's compound 2a and took another approach to solve the problem. In his attempt using a silver benzoate displacement reaction on D-glucose diethyl dithioacetal, Fletcher prepared in very low conversions 2-O-benzoyl-β-D-glucose, which was isolated as its tetraacetate. A similar treatment of ethyl-1-thio-β-D-glucopyranoside gave after acetylation both 1,3,4,6-tetra-O-acetyl-2-O-benzoyl-α-D-glucopyranose and 2,3,4,6-tetra-O-acetyl-1-O-benzoyl-β-D-glucopyranose (6). Although, the 1-α-D-glucosyl ester was apparently an initially formed product, ester migration to the 2-position evidently took place upon isolation. Successful preparation of a stable 1-O-α-D-glucosyl ester, which did not undergo migration, was finally realized in the synthesis of the hindered mesitoate derivative 2b in 17% yield (6).



Although 2b was stable to neutral conditions, it could be induced to undergo C_1 to C_2 ester migration under basic conditions (7). It was concluded (6) that 2b would be "the only example of a cis-1-O-acylaldose that could be prepared and isolated" without rapid rearrangement. Preparation of the 1-O-acyl-β-D-glucopyranoses 1β is less complex because of the inability of the trans



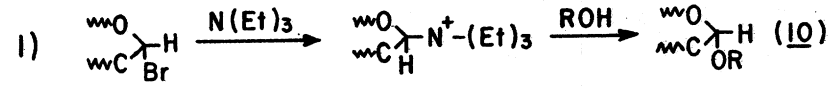
3, X = Na, Li
4, X = H

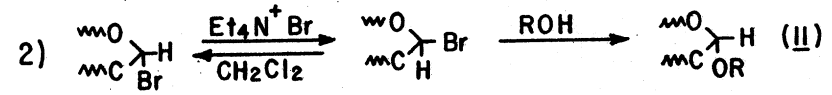
oriented 1-O-acylaldose to undergo analogous ester shifting. Acylation of partially protected 4,6-O-benzylidine-1-O-sodio-D-glucopyranose 3 yielded 1b after deblocking (8). Nevertheless, overall conversions of the anomerically pure product ester 1b based on glucose were only 30-40% due to the low and variable results obtained for the isolation and purification of 4,6-O-benzylidine-D-glucopyranose 4 and its corresponding salt 3.

In this report we will describe some new synthetic approaches to the preparation of glucosyl esters 1a and 1b, and examine their spectral properties and chemical reactivity including acyl migration. We will also discuss the mechanistic implications which are important in explaining the stereochemical control achieved in the key acylation reaction.

Stereoselective Acylation of 2,3,4,6-tetra-O-benzyl-1-O-lithio-D-glycopyranose (TBG^-Li^+) (9)

One of the most elegant methods for achieving stereoselective glycosidation has recently been demonstrated by Schuerch (10), equation 1, and Lemieux (11), equation 2. Utilizing 2,3,4,6-tetra-O-benzyl-1-bromo-α-D-glucopyranose (TBGB), these workers carried out double inversion displacement reactions in which the final glycoside linkage had the desired configuration. Equation 1

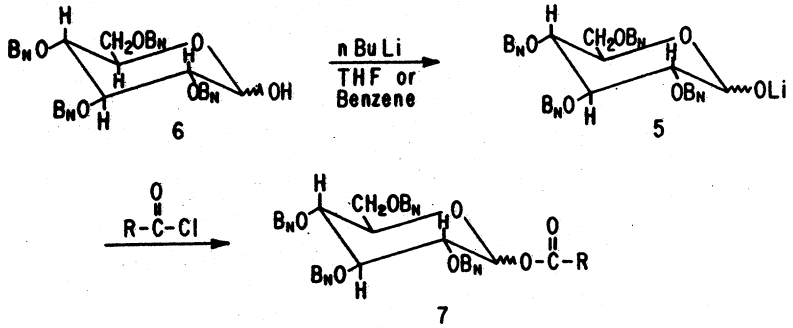




depicts stereochemical control through the agency of the "reverse anomeric" effect exhibited by the equatorial preference of ammonium salt intermediate (10), while equation 2 demonstrates the approach through equilibration effected by solubilized bromide ion. In each case a high selectivity for α-glycoside linkage formation was shown. However, in the early stages of the latter reaction (equation 2) a preference for the β-anomer could be realized, but overall conversion to this species was low. For the study of the acylation of the anomeric OH of glucose, we examined the reactions of 2,3,4,6-tetra-O-benzyl-1-O-lithio-D-glucopyranose 5 (TBG^-Li^+) because of its nonparticipating group at the C_2 position. Furthermore, if stereoselective acylation could be carried out directly on 5, it would obviate the need to prepare the unstable bromide derivative TBGB (11) for an indirect displacement reaction.

Metalation of 2,3,4,6-tetra-O-benzyl-D-glucopyranose (TBG) 6 (10 mmol) in 125 ml of tetrahydrofuran (THF) at -30 to -40° with

1.1 equivalents of n-butyl lithium (1.6 M in hexane) followed by acylation with 1.1 equivalents of acyl halides, (20 minutes) produced a mixture of 2,3,4,6-tetra-O-benzyl-1-O-acyl-D-gluco-pyranose esters (TBG esters) 7α and β in 90-95% yield with a



6 5 7

decided preference for the α-configuration 7α. Often the isolated products were oils which could not be crystallized; however, the anomeric composition was easily determined by evaluation of the proton nmr spectrum of the characteristic anomeric hydrogens. Table I lists the physical properties of esters prepared by this procedure. For each member in this series, the anomeric composition of the isolated product esters was always at least 90% α and 10% β by nmr analysis. However, selectivity for the α-anomer diminished (70% α, 30% β) with acylation temperature elevation to 60°. Metalation of 6 in benzene at 0-5°C followed by acylation at this temperature produced a mixture of esters 7α and 7β, containing equal amounts of both α- and β-anomeric forms. At higher temperatures, ∿60°, we observed unexpectedly high selectivity for the production of the β-anomeric ester 7β. In all cases studied at ∿60° we obtained products with a β/α ratio of 9/1, a complete reversal of the selectivity shown in THF at -30°. Table II contains physical properties of ester products obtained from acylation of 5 in benzene at 60°. This stereoselectivity is much greater than previously reported. For example, the direct acylation of 6 in methylene chloride-pyridine over a wide range of temperatures gives only slight selectivity for formation of the α-anomer (60-70% α, 30-40% β) (12) as does the dehydration-acylation reaction with the N-acylamino acid facilitated by dicyclohexylcarbodiimide (13).

To establish the mechanism responsible for the stereoselective control of this reaction we studied the products as a function of solvents and temperature using a single acylating agent. Table III shows the results obtained through acylation of 5 with hexadecanoyl chloride in benzene and in THF at temperatures from -40° to +62°C. As previously noted in the THF, the α-glycosyl ester 7α is the predominant product over the temperature range of -40° to +60°. However, selectivity for the α-anomer decreased (70% α, 30% β) when the reaction temperature was raised to 25°, and

Table I. Acylation Products of TBG$^-$Li$^+$ in THF at -30 to -40°C[a]

R	ir, C=O, cm^{-1}	δ (ppm) C_1-H,J (Hz) α-anomer	β-anomer	$[\alpha]_D^{25}$ (CH_2Cl_2, 1c)
$C_{17}H_{35}$[b]	1745[c]	6.65(d,2.6)	5.85(d,6.8)	+39.2
$C_{15}H_{31}$[b]	1745[c]	6.65(d,2.6)	5.85(d,6.8)	+45.9
cis-9,$C_{17}H_{33}$[b]	1750[c]	6.65(d,2.6)	5.85(d,6.8)	+42.8
phenyl[d]	1740[e]	6.70(d,3.3)	5.90(m)[f]	+73.5
p-nitrophenyl[g]	1737[e]	6.60(d,3.3)	5.90(m)[f]	+72.0
2,4,6-trimethylphenyl	1740[e]	6.66(d,2.7)	5.90(m)[f]	+73.7

[a]All products are 90% α-anomer, 10% β except where otherwise indicated, rotations are for pure α-anomers when recrystallization was possible.

[b]Noncrystallizable glasses.

[c]Neat films.

[d]mp of recrystallized product 84-85 (EtOH).

[e]Chloroform solution.

[f]ABX multiplet.

[g]mp of recrystallized product 124.2-125.0 (EtOH).

Table II. Acylation Products of $TBG^{-}LI^{+}$ in Benzene at 60°[a]

R	ir, C=O, cm^{-1}	δ, (ppm) C_1-H,J (Hz) α-anomer	δ, (ppm) C_1-H,J (Hz) β-anomer	$[\alpha]_D^{25}$ (CH_2Cl_2,1c)
$C_{17}H_{35}$[b]	1750	6.65(d,2.6)	5.85(d,6.8)	+10.7
$C_{15}H_{31}$[c]	1750	6.65(d,2.6)	5.85(d,6.8)	+ 9.1
phenyl[d]	1735	6.70(d,3.3)	5.90(m)[e]	-23.0
2,4,6-trimethylphenyl[f]	1740	6.66(d,2.8)	5.90(m)[d]	+ 1.6
p-nitrophenyl[g]	1737	6.60(d,3.3)	5.90(m)[d]	-27.0[h]

[a]All products were 90% β, 10% α, rotations are for pure β-anomers when recrystallization was possible.

[b]Noncrystallizable glass.

[c]mp of recrystallized product 52-53 (EtOH).

[d]mp of recrystallized product 96.0-97.2 (cyclohexane).

[e]ABX multiplet.

[f]mp of recrystallized product 131.0-1.5 (EtOH).

[g]mp of recrystallized product 96-98, see reference 12.

[h](Dioxane, 6 c) reference 12.

Table III. Stereochemical Distribution of Anomeric 1-O-Hexadecanoyl-D-TBG as a Function of Temperature and Solvent

Solvent	α	Temperature	$[\alpha]_D^{25}$ (CH_2Cl_2, 1c)

Table III. Stereochemical Distribution of Anomeric 1-O-Hexadecanoyl-D-TBG as a Function of Temperature and Solvent

Solvent	α	β	Temperature	$[\alpha]_D^{25}$ (CH_2Cl_2, 1c)
THF	90%	10% (via pmr)[a]	-30 to -40°	+45.9
"	70	30	25°	+39.2
"	70	30	45°	-
"	70	30	60°	+36.0
Benzene	50	50	0 to 5°	+27.8
"	26	74	40 to 45°	+20.6
"	11	89	62°	+14.9
" + 4% HMPA	70	30	62°	+35.0

[a]Derived from the integration of the anomeric protons.

seemed to remain constant above this temperature. Overall conversions tend to drop from 95% to 85% with prolonged heating. In benzene, acylation selectivity exhibits more sensitivity to temperature change. The high selectivity for 7β formation at elevated temperature (62°), decreases with decreasing temperature (limiting temperature is the freezing point of benzene). Addition of 4% of a highly polar aprotic solvent, hexamethyl phosphoramide (HMPA), reversed the product distribution in benzene at 62°C to give the same product distribution observed in THF at 25°. Figure 1 depicts the rotation of 1-O-hexadecanoyl-D-TBG esters as a function of the α/β ratio. Although we have been unable to isolate the 1-O-hexadecanoyl-α-D-TBG in high purity owing to the noncrystalline nature of the reaction product, by extrapolation of the data of Figure 1 we obtain a rotation value of +51.0 for the pure α material.

Concerning the Structure of TBG, $TBG^{-}Li^{+}$, and the Mechanism of Acylation

That TBG 6 mp 152-153° exists in the α-configuration is well documented (11, 12, 14, 15). However, this fact is inconsistent with the observations that the stereochemistry of its acylation products vary so widely. For this reason our first task was to reexamine the stereochemistry of TBG. In studying the proton spectrum of TBG, earlier workers (14) had failed to observe that the α-anomeric proton resonance does not account for a single proton relative to the other protons in the molecule. We observed that the measured intensity of this resonance relative to all other proton resonances in TBG reflects only a fraction of the anomeric composition. This mixed anomeric composition may also be verified by measurement of the anomeric OH resonance in a slow OH exchanging ether solvent such as THF-d_8. Examination of TBG in various aprotic solvents by 220 MHz proton nmr spectroscopy confirmed that TBG is an anomeric mixture. Table IV lists the anomeric composition of TBG in four aprotic solvents. In each solvent except for chloroform, the anomeric composition appeared to be very similar. This is also borne out by the rotational data (Table IV). These data support the idea that crystalline TBG apparently exists as a eutectic mixture or solid solution of α and β forms, since instantaneous mutarotation in aprotic media would be highly unlikely. In addition, the equilibrium concentrations of TBG found in THF and benzene do not reflect the acylated product distributions of 7α and 7β in these respective solvents. An a priori explanation for the acylation product distribution might be based on a solvent dependent equilibration between the anomeric metalated species 5α and 5β. Thus, we might expect a predominance of anomer 5α in THF and a predominance of 5β in benzene in accord with the observed acylation product distribution. However this does not turn out to be the case. To examine this

Table IV. Anomeric Composition of TBG by 220 MHz H'NMR and Rotational Measurements

Solvent	[a] $[\alpha]_D^{25}$	α-anomer δ C_1-H ppm, J(Hz)		β-anomer δ C_1-H ppm, J(Hz)		fraction[b] % α
pyridine d_5	+55.0	5.89	d,3.0	5.45	d,11.0	52[c]
THF d_8	+46.8	5.20	brs	5.0	d,10.5	50[d;f] 67[d]
Benzene d_6	+53.6	5.23	d,3.0	-[e]		59[f]
Chloroform d_1	+19.1	5.12	d,3.0	-[e]		65[f]

[a] 0.100 g/10 ml of solvent.

[b] Spectra taken at 17° except where indicated otherwise.

[c] Composition was confirmed by comparison of the α and β-OH resonances observed at 5.9 δ and 5.38 δ, respectively.

[d] Measurement made at 55°.

[e] Could not be observed.

[f] Fraction estimated from comparison of the area of the anomeric proton resonance with the area of the remaining protons in molecules.

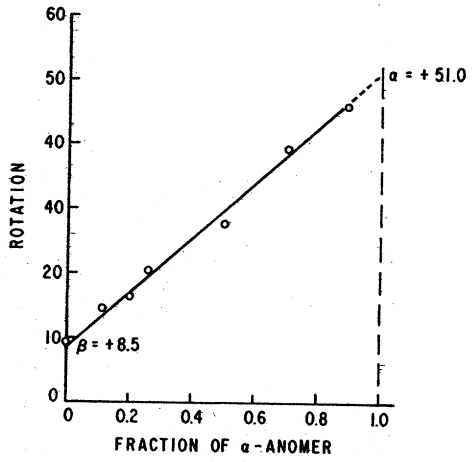


Figure 1. Plot of the α,β composition of 1-O-hexadecanoyl-D-TBG against observed rotation $[\alpha]_D^{25}$ (CH_2Cl_2, 1c)

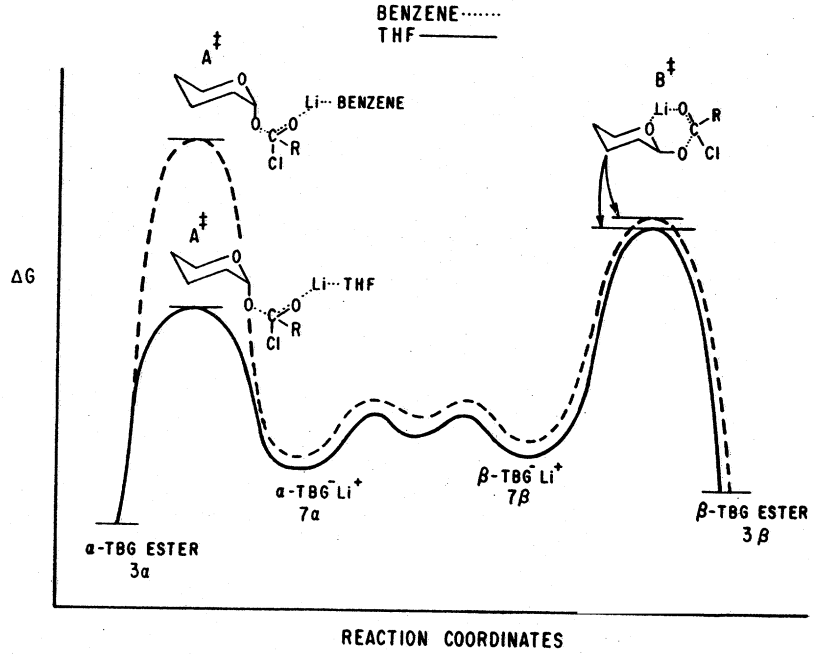
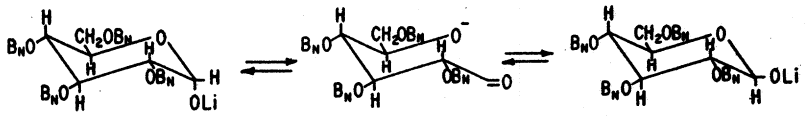


Figure 2. Pathway for the reaction of α- and β-TBG Li⁺ with acid chlorides in benzene and THF

hypothesis we measured the equilibrium concentrations of 5α and 5β in the two reaction solvents.



5α 5β

An attempt to evaluate the composition of 5 in both THF-d_8 and benzene-d_6 by proton nmr met with failure due to inordinately broad resonances. However, examination of the low frequency ^{13}C spectrum showed narrow lines which were readily assignable to the respective anomeric carbons. Samples were prepared by the addition of one equivalent of n-butyl lithium in hexane to a dried degassed solution (2 ml), containing 150 mg of 6 in a 10 mm nmr tube. The spectra were recorded at 22.63 MHz on a ^{13}C FT spectrometer. Ten second delay times were utilized between scans to allow for differences in T_1 relaxation times and to assure quantitation resonance absorption responses, (relaxation times (T_1) have been observed to be never more than 1.5 seconds) (16). Table V gives the ^{13}C chemical shifts and intensities of the anomeric carbons for 6 and 5 in benzene-d_6 and THF-d_8. The C_1 carbon of the β-anomer 6β is observed at lower field than the C_1 of the α-anomer 6α (17). The α/β ratio agreed well with the data obtained by proton nmr (see Table IV). Upon metalation each of the respective C_1 carbons underwent a 3 ppm upfield shift due to the shielding effect of the negative charge on oxygen (18). Only a small change in the anomer distribution was observed, i.e., the α anomer contribution decreased from 61% and 67% in benzene and THF, respectively, to 50% and 52% in the metalated forms. Apparently there are no significant differences in the equilibrium concentrations of either anomeric forms of TBG$^-$Li$^+$, 5α or 5β, in either reaction solvent. The stereochemical selectivity of this reaction must, therefore, be controlled by the relative velocity with which either of these two species 5α and 5β are acylated. Figure 2 shows postulated relative energies of the various solvated activated complexes that might account for the observed

Table V. Anomeric Composition and ^{13}C Chemical Shifts

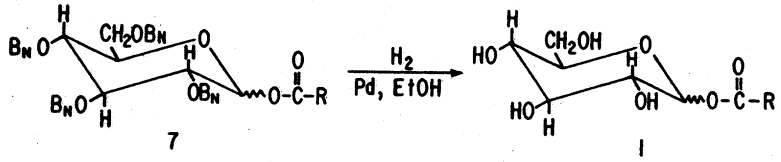
	δ Benzene		δ THF		% α	% α
	α	β	α	β	Benzene	THF
TBG	91.3	98.2	91.6	98.6	61	67
TBG$^-$Li$^+$	89.1	95.9	88.8	96.1	50	52

product outcome. In THF solution, the lower energy pathway provided by solvent-solvated $A^{\neq}$ relative to the higher energy pathway given by internally solvated $B^{\neq}$ leads to a predominance of product 7α. Conversely, in benzene intramolecular coordination of $B^{\neq}$ is favored since it offers greater stabilization relative to the stabilization imparted to $A^{\neq}$ by the relatively nonpolar, poorly solvating benzene. Therefore, in benzene, product 7β predominates. Increase in the polarity of the benzene solution with as little as 4% v/v HMPA, (Table III) permits the formation of a low energy HMPA intermolecularly solvated transition state $A^{\neq}$ leading to product 7α.

In the absence of kinetic data we can only speculate on the effect of temperature on product distribution. However, we can see that in both solvents, increased temperature is associated with an increase in the reaction through pathway $B^{\neq}$ to produce more 7β. This temperature effect appears consistent if we assume a high $\Delta S^{\neq}$ for transition state $B^{\neq}$ relative to $A^{\neq}$ due to the latter's ordering of solvent molecule. Thus, as the temperature is increased in both solvent systems, the $T\Delta S^{\neq}$ term could become dominant (more positive), effectively lowering even further the $\Delta G^{\neq}$ for the pathway through transition state $B^{\neq}$ relative to pathway through $A^{\neq}$.

1-O-Acyl-D-Glucopyranoses 1α and 1β

Both products 7α and 7β from acylation in THF and benzene, respectively, underwent final purification by elution from a column of Florisil with methylene chloride-petroleum ether. (Reference to brand or firm name does not constitute endorsement by the U.S. Department of Agriculture over others of a similar nature not mentioned.) Each was then hydrogenated (40 psi) in



ethanol with palladium black for eight hours. In most cases we found prior chromatographic purification essential for successful deblocking. On some occasions, addition of a few drops of acetic acid was necessary to catalyze the hydrogenolysis. Although the protected esters 7α and 7β were 90:10 anomeric mixtures which in most cases were not separable, the deblocked esters 1α and 1β could easily be recrystallized to produce both pure α- and β-forms in 70-85% yield. In contrast to the finding of previous reports (6, 7), we observed the 1-α-D-glucosyl esters 1α to be

Table VI. Physical Properties of 1-Glucosyl Esters 1α, 1β

R	Configuration	mp	ir, ($CHCl_3$) C=O, cm^{-1}	δ C_1-H ppm[a], J(Hz)	$[\alpha]_D^{25}$
$C_{16}H_{31}$	α	98-108[b]	1742	6.48 d,3.0	66.9 (MeOH, 0.9c)
$C_{16}H_{31}$	β	108, 170-5[b]	1725	5.65 d,6.8	-1.17 (MeOH, 1.2c)
$C_{18}H_{35}$	α	112-121[b]	1742	6.48 d,3.0	+72.9 (MeOH, 1c)
C_6H_5	α	c	1720	6.55 d,3.0	+85.2 (H_2O, 0.36c)
C_6H_5	β	192-3[a]	1712	5.90 m	-27 (HO, 0.45c)
CH_3	α	c	1740	6.27 d,3.0	-
2,4,6-trimethylphenyl	α	166-9[d]	1725	6.40 d, 3.0	+102 (H_2O, 0.50c)
2,4,6-trimethylphenyl	β	153-9[d]	1729	5.75 m	
cis-9, $C_{17}H_{33}$	β	c	1725	e	+59.0 (MeOH 0.9c)
cis, cis-9,11 $C_{17}H_{31}$	β	c	1725	e	+51.0 (MeOH, 0.9c)

[a]Spectra obtained at 60 MHz in CD_3OD (sealed tubes at 76°) because of the insolubility of the derivatives.

[b]Recrystallized from cnloroform-hexane.

[c]Unable to crystallize these derivatives.

[d]Recrystallized from EtOH.

[e]Anomeric proton resonance coincided with the double bond proton resonances.

relatively stable, giving rise to rearrangement only after prolonged heating. Further details of this acyl migration will be elaborated on in the last section. Table VI lists the physical properties of the isolated 1α and 1β esters.

The configuration of each of these materials was established by both ^{1}H and ^{13}C nmr except for the unsaturated esters where ^{13}C could only be used because of overlapping resonance signals in the proton spectra. Figures 3A and 3B illustrate typical ^{13}C spectra of 1α and 1β derived from long chain saturated carboxylic acids. As is observed for the parent glucose molecule, the α-anomeric carbon C_1 absorbs at a higher field than the β-C_1 carbon (17), yet the difference in chemical shift between α-C_1 and β-C_1 is only 2 ppm compared to the 4 ppm noted for glucose (17). The smaller difference in field positions is likely due to induced upfield shielding of the β-C_1 relative to the α-C_1 by the ester carbonyl. Shielding of 2.2 ppm is also evident in the C_2 resonance of 1α, presumably because of orientation with respect to the carbonyl whereas C_2 of 1b is deshielded by 1.6 ppm. A comparison of the hexose ring ^{13}C shifts for 1α and 1β and glucose is given in Table VII. The anomeric purity of each compound was verified by glc analysis of the corresponding trimethylsilyl derivatives on a 6' 1/4" O.D. glass column packed with 3% SP2100 and programmed from 180-250° at 6°/minute. Under these conditions each of the isomeric α- and β-pairs could be readily separated, the β-anomer having the longer retention time. Typical retention times for the α- and β-hexadecanoate esters were 12.0 and 12.5 minutes, the α- and β-mesitoates, 8 and 8.2 minutes, respectively.

Table VII. Hexose Ring ^{13}C Shifts for α and β-D-Glucose and Corresponding 1-Hexadecanoyl Esters

	Carbon Shifts (ppm)[a]					
	C_1	C_2	C_3	C_4	C_5	C_6
δ-D-Glucose[b]	92.8	72.3	73.6	70.4	72.3	61.6
β-D-Glucose[b]	96.7	74.9	76.7	70.4	76.5	61.6
1-α-D-Glucosylhexadecanoate[c]	92.2	73.9	74.2	69.7	71.0	61.4
1-β-D-Glucosylhexadecanoate[c]	94.3	72.7	76.8	69.9	76.8	61.7

[a] All shifts relative to TMS as internal standard.

[b] Spectra taken in D_2O.

[c] Spectra taken in 50/50 v/v $CDCl_3$, CD_3OD.

Alternate Routes to 1-O-Acyl-D-glucopyranoses Derived from Unsaturated Carboxylic Acids

To prepare 1-D-glucosyl esters derived from unsaturated carboxylic acids, a second pathway was needed since the method mentioned above required a final reductive step to remove all

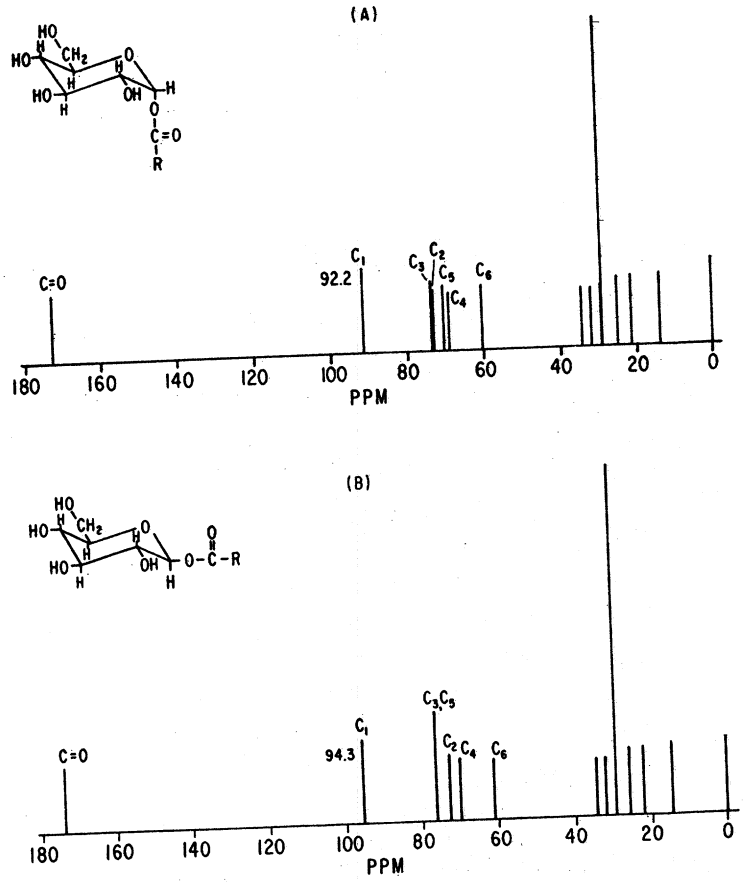
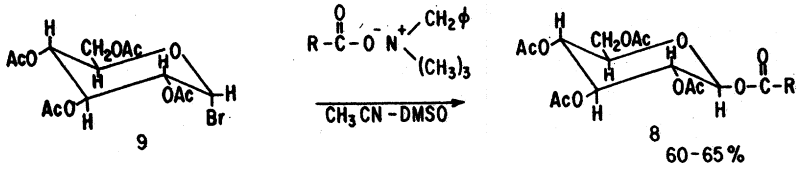


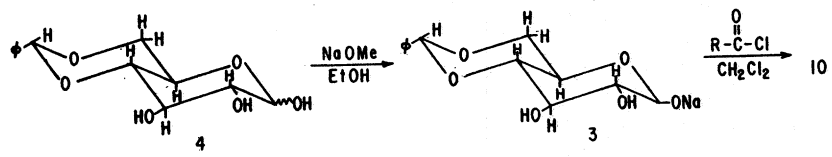
Figure 3. ^{13}C *spectra of* (A) *1-α-D-glucosyl hexadecanoate and* (B) *1-β-D-glucosyl hexadecanoate were taken at 22.63 Hz using 150 mg of sample in 2 ml of 50/50 v/v* CD_3OD–$CDCl_3$ *at 50°C. The spectra were obtained on a Fourier Transform nmr spectrometer after 700 transients with a 5 sec delay time. All shifts are relative to internal TMS.*

blocking groups. Our first approach at solving this problem was the preparation of 2,3,4,6-tetra-O-acetyl-1-O-acyl-β-D-glucopyranose 8 through displacement of the corresponding bromide 9 (19). This was easily accomplished by reaction of 9 with the benzyl-trimethyl ammonium salt of either octadecanoic or cis-9-octadecenoic acid in 65:35 DMSO-CH_2Cl_2 at 50° for 24 hours.



After workup and chromatographic purification of the reaction mixture through a Florisil column with CH_2Cl_2-petroleum ether, we obtained 60-65% of pure ester 8 with the β-configuration. Nmr in $CDCl_3$ showed the characteristic anomeric proton resonance at 6.0δ d, J = 6.5 Hz, ir, C = O 1750 cm^{-1}, rotation -1.5 (MeOH), 1 C). The melting point of the octadecanoate was 69-70°, (lit. mp 77° (20)), whereas the octadecenoate was a viscous oil. Both compounds provided the correct elemental analyses. Attempted deacetylation of these compounds with either barium hydroxide (21) or sodium hydroxide in methanol at temperatures as low as -40° failed to show preferential removal of acetate over the long chain acyl group. Even the ammonia in methanol deacetylation described by Robert (22) for the preparation 1-β-D-glucosyl anthranilate resulted in unselective deacylation. The latter procedure appears to be applicable to the removal of acetate only in the presence of less reactive aromatic esters.

The pathway selected for the preparation of the unsaturated glucosyl esters 1 employs 4,6-O-benzylidine-D-glucose 4 (23). Preparation and isolation of the dried sodium salt of 4,6-O-benzylidine-D-glucose 3 from ethanol solution followed by



acylation in CH_2Cl_2, (heterogeneous mixture) led to 4,6-O-benzylidine-1-O-acyl-D-glucopyranose 10 in 40-50% isolated yield based on 4 (8) (overall yields based on glucose were more variable because the yields in preparing 4 ranged from 20-80%).

The stereochemistry of these derivatives was studied by both ^1H and ^{13}C nmr. Figure 4 shows how the anomeric proton resonance which coincides with the chemical shift of the benzyl hydrogen in 10 is shifted downfield with the incremental additions of $Eu(fod)_3$ pseudocontact shift reagent. Judging from the initial chemical shift of the anomeric proton (5.8δ) and coupling constant, 7.5 Hz, the hexadecanoate ester has the β-configuration. In studying this acylation reaction, we observed that as the acylation reagent became more unsaturated the reaction became less stereoselective, e.g., acylation of 3 with hexadecanoyl chloride or octadecanoyl chloride gave effectively 100% of the β-isomer while cis-9-octadecenoyl chloride gave 90% β; cis,cis-9,12-octadecadienoyl chloride, 85% β; and the cis,cis,cis-9,12,15-octadecatrienoyl chloride, 60% β (Table VIII). Measurement of the isomer ratio was routinely performed by ^{13}C nmr because of the difficulty in directly observing the β-anomeric proton in the absence of shift reagent as mentioned above. Comparison of the C_1 anomeric carbon resonances at 92.2δ (α) and 94.1δ (β) provided a direct analysis of the stereoselectivity of the reaction. The isomer ratios were also confirmed by glc analyses of the corresponding TMS derivatives.

Table VIII. Stereoselectivity of Acylation of 1-O-Sodio-4,6-O Benzylidine Glucose as a Function of the Degree of Unsaturation in the Acylating Agent

R	mp[a]	anomeric % α	composition[b] % β
$C_{17}H_{35}$	132-3	0	100
$C_{15}H_{31}$	131-131.8	0	100
cis-9,10 $C_{17}H_{33}$	-[c]	10	90
cis,cis-9,12, $C_{17}H_{31}$	-[c]	15	85
cis,cis,cis-9,12,14, $C_{17}H_{29}$	-[c]	40	60

[a] All esters had C=O absorption at 1755 cm^{-1} ($CHCl_3$).

[b] All compositions determined by ^{13}C nmr comparison of the anomeric carbon resonances prior to recrystallization.

[c] Viscous glass.

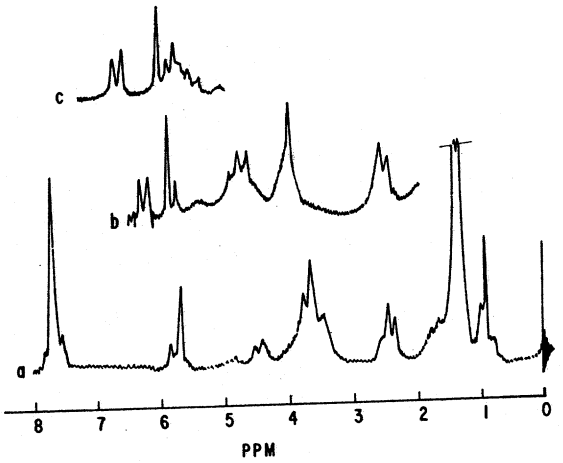


Figure 4. Low field 60 MHz proton spectrum of 1-O-hexadecanoyl-4,6-O-benzylidine-β-D-glucopyranose (0.04 g in 0.400 ml of $CDCl_3$). (a) Spectrum in the absence of Eu(fod)$_3$ solution; (b) after addition of 15 ml of 0.30 M Eu(fod)$_3$ solution in CCl_4; (c) after addition of 20 ml of 0.30 M Eu(fod)$_3$ solution in CCl_4.

The ^{13}C spectrum of the isomeric mixture of 1-O-cis,cis-9,12-octadecadienoyl-4,6-O-benzylidine-D-glucopyranose is shown in Figure 5a. Assignments at all ring carbons could not be readily made owing to the unpredictable changes in chemical shifts imposed by the acetal bridging. Nevertheless the α/β ratio at the anomeric center as well as the cis/trans ratio was easily determined. Because of the alkalinity of the reaction medium, we observed as much as 5-7% trans product at acylation temperatures of -30 to -40°. Comparison of the C_8 and C_{14} resonances, (external allylic carbons associated with an adjacent cis double bond) at 27.3δ with the C_8 and C_{14} resonances at 32.6δ, associated with the trans double bonds, yielded the cis/trans ratio directly.

At present we cannot explain why an increase in the degree of unsaturation of the acid chloride caused a decrease in stereoselectivity. However, one possible cause may be solubility changes taking place in the heterogeneous acylation reaction mixture due to structural differences in the various polyunsaturated acid chlorides used. Acylation of both sodium and lithium salts 3 generated in situ homogeneously from either sodium or n-butyl lithium in THF at -30° gave varying product distributions, i.e., ester mixtures composed of 50-60% 9b, 20-25% 9a, and 15-20% acyl migrated compounds 12. Presumably, 3 when isolated in crystalline form, assumes the β-configuration 3β which when acylated in a nonsolubilized form yields 10β. However, as the solubility of 3 is increased, either by solubilizing agents, i.e., polyunsaturated acid chlorides or by generation in soluble form in situ, equilibration of the anomeric salts 3α and 3β can occur. Unlike TBG^-Li^+ 5, no change in the distribution of isomeric acylation products is noticed when benzene is substituted for THF. This difference in behavior is probably a reflection of participation by free C_2-OH which is made unavailable in TBG through ether protection.

β-Glucosyl esters 1b derived from unsaturated carboxylic acids were readily generated from 9b by hydrolysis in 75% acetic acid-water at 60° for one hour (24). Yields of isolated and purified (silica gel chromatographed) esters 9β were in the range of 40-50% based on glucose. The ^{13}C spectrum of 1-O-cis,cis-9,11-octadecadienoyl-D-glucopyranose (85% α, 15% β) is seen in Figure 5b. Other physical properties of the unsaturated esters are given in Table VI.

Stability of 1-O-Acyl-α-D-Glucopyranose Derivatives

In several attempts to prepare 1-O-acyl-α-D-glucopyranose 1α, it has been reported that isolation could not be accomplished (6, 7). Only when the ester was highly hindered, e.g., the mesitoate derivative 2a, could the compound be isolated in the unmigrated state. The previous attempts to generate 1α and 1β (through deblocking precursor compounds containing acyl protecting groups) were carried out in basic solution. This caused acyl

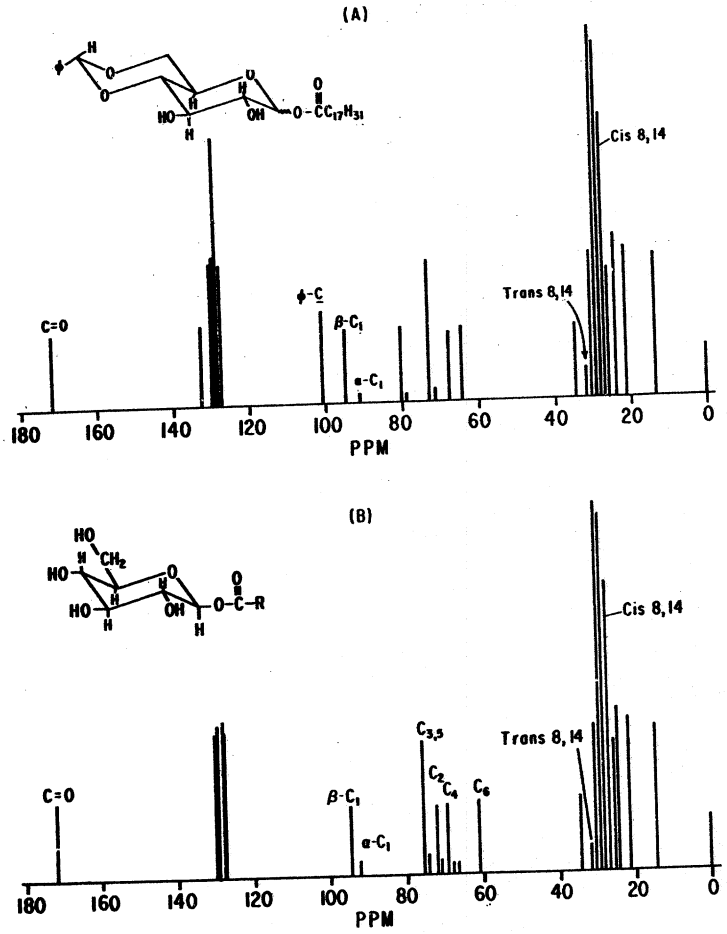
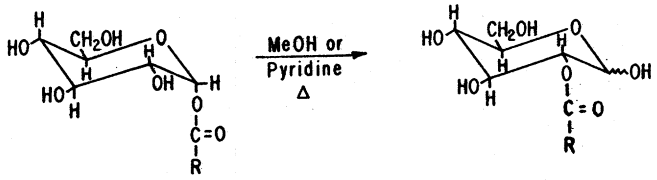


Figure 5. (A) ^{13}C *spectrum of 0.150 g of* cis,cis-9,12-octadecadienoyl-α,β-4,6-O-benzylidine glucose *in* $CDCl_3$. *Chemical shifts relative to internal TMS.* (B) ^{13}C *spectrum of 0.150 g of* cis,cis-9,12-octadecadienoyl-D-gluco-pyranose (85% β, 15% α).

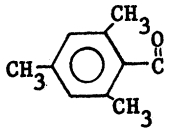
migration and saponfication. We have successfuly deblocked 7α by hydrogenolysis in neutral or slightly acid medium. This has permitted us to isolated pure, unrearranged 1α. Although 1-O-acyl-α-D-glucopyranoses 1α are stable in the crystalline state, they



1α 12

slowly rearrange upon prolonged heating in neutral solution or upon melting on a glass surface. Rearrangement of 1α was studied in methanol and pyridine by proton nmr. The progress of acyl migration of the hexadecanoate derivative in CD_3OD at 76° is illustrated in the spectrum shown in Figure 6. Appearance of the anomeric proton resonances at the high positions of 5.5δ and 4.7δ is indicative of the formation of the isomeric mixture of free C_1-OH glucopyranoses 12α and 12β esterified at C_2. The detailed 220 MHz proton spectrum of 12α and 12β in pyridine-d_5, (Figure 7) identifies the migration products as the C_2-OH esterified product by its characteristic H-C-O-acyl shift pattern and field position

Table IX. Migration Rates of 1-O-Acyl-α-D-glucopyranoses and Rotations of the Product 2-O-Acyl-D-glucopyranoses

R	Methanol $k_{76}^a \times 10^2 min^{-1}$	Pyridine $k_{76}^a \times 10^2 min^{-1}$	$[\alpha]_D^{25}$
$C_{15}H_{31}C(=O)$	2.8	1.0	+34.6 (MeOH, 0.6c)
$C_6H_5C(=O)$	3.0	-	+41.5 (H_2O, 0.96c)
	No reaction	No reaction	+44.5[b] (H_2O, 0.4c)

[a]Measured by following the disappearance of the anomeric proton of the 1-O-acyl-α-D-glucopyranose and the appearance of the α and β anomeric protons of 2-O-acyl-D-glucopyranose products.

[b]Reference 7.

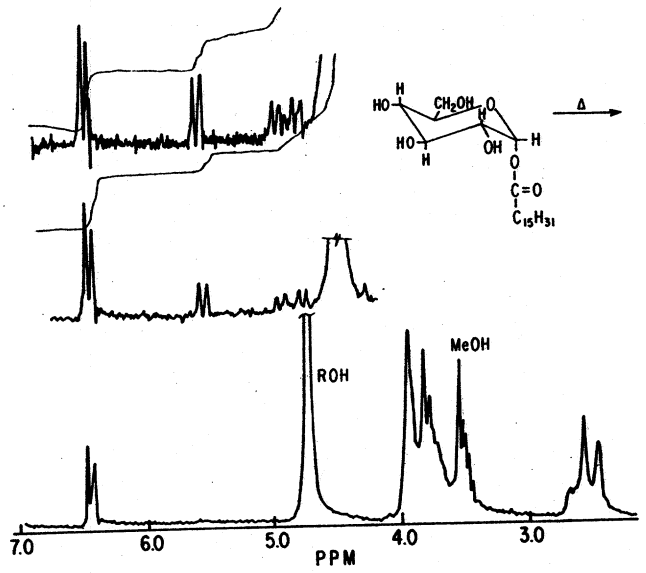
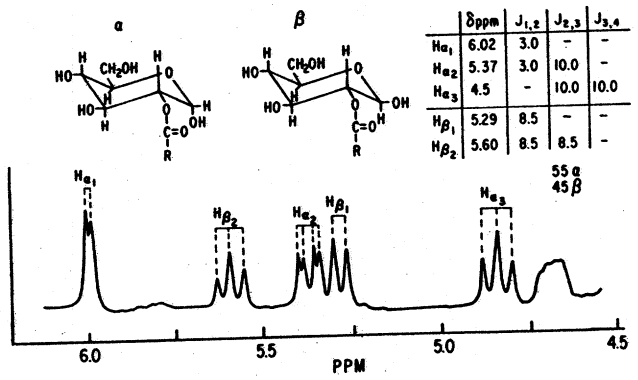


Figure 6. 60-MHz nmr spectrum of 1-O-hexadecanoyl-α-D-glucopyranose in CD_3OD during acyl migration at 76°C. All shifts are relative to internal TMS.



	δppm	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$
H_{α_1}	6.02	3.0	–	–
H_{α_2}	5.37	3.0	10.0	–
H_{α_3}	4.5	–	10.0	10.0
H_{β_1}	5.29	8.5	–	–
H_{β_2}	5.60	8.5	8.5	–

Figure 7. 220-MHz nmr spectrum of 2-O-hexadecanoyl-D-glucopyranose (region from 4.5–6.2δ) in pyridine-d_5. All shifts are relative to internal TMS.

(25). Integration of the α and β anomeric protons shows this mixture to be 55% 12α and 45% 12β. Rearrangement rates at 76°, given in Table IX, are first order in ester 1α in methanol and pyridine, the rate in the former being somewhat faster. Both aliphatic and unsubstituted aromatic esters migrate at the same rate. The mesitoate derivative is stable under these conditions. Significantly, although migration readily occurred at 76° in methanol and pyridine, no acyl migration was observed in the presence of 8.0 mole % acetic acid at 76° after 24 hours. Reaction rates in both teflon as well as quartz nmr tubes were the same as those observed in pyrex, indicating that active sites in the glass were not responsible for catalyzing this process.

Summary

The stereoselectivity of acylation of TBG$^-$Li$^+$ is effectively controlled by altering the solvent medium and temperature. The blocking benzyl ether groups were removed by hydrogenolysis to produce both stable 1-α and 1-β glucosyl esters derived from saturated carboxylic acids. TBG and its salt TBG$^-$Li$^+$ were found by nmr to be an equilibrium mixture of both α and β-anomeric forms. A mechanism concerning the stereochemical control of TBG$^-$Li$^+$ acylation is discussed in terms of inter and intramolecularly solvated transition states. Glucosyl esters of unsaturated carboxylic acids were prepared through the acylation of 4,6-O-benzylidine-1-O-sodio glucopyranose. Stereoselectivity of acylation dropped off with an increase in the degree of unsaturation in the acylating agent. Acylation of both 1-O-lithium and sodium salts of 4,6-O-benzylidine glucose generated in homogeneous solution yielded mixtures of 1-α- and β-glucosyl esters and acyl migration products. The stability, kinetics, and products of acyl migration of 1-α-glucosyl esters were examined.

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Literature Cited

1. Quilico, A., Piozzi, F., Pavan, M., and Mantica, E. Tetrahedron (1959) 5, 10.
2. Wood, H. B., Jr., Allerton, R., Diehl, H. W., and Fletcher, H. G., Jr. J. Org. Chem. (1955) 20, 875.
3. Polonsky, J., Sach, E., and Lederer, E. Bull. Soc. Chim. France (1959) 880.
4. Fischer, E., and Bergmann, M. Ber. (1918) 51, 1760.
5. Schmidt, O. Th., and Herok, J. Ann. (1954) 587, 63.

6. Pedersen, C., and Fletcher, H. G., Jr. J. Amer. Chem. Soc. (1960) 82, 3215.
7. Wood, H. B., and Fletcher, H. G., Jr. J. Amer. Chem. Soc. (1956) 78, 2849.
8. Fletcher, H. G., Jr. In "Methods in Carbohydrate Chemistry" VI, 231, Academic Press, New York, 1972.
9. A preliminary report of this acylation method has been reported by Pfeffer, P. E., Rothman, E. S., and Moore, G. G. J. Org. Chem. (1976) in press.
10. West, A. C., and Schuerch, C. J. Amer. Chem. Soc. (1973) 95, 1333.
11. Lemieux, R. U., Hendriks, K. B., Stick, R. V., and James, K. J. Amer. Chem. Soc. (1975) 97, 4056.
12. Glaudemans, C. P. J., and Fletcher, H. G., Jr. In "Methods in Carbohydrate Chemistry" VI, 373, Academic Press, New York, 1972.
13. Valentekovic', S., and Keglevic'. Carbohydrate Res. (1976) 47, 35.
14. Volkova, L. V., Luchinskaya, Karimoua, N. M., and Evstigneeva, R. P. Zh. obs. Khim. (1972) 42, 1405.
15. Schmidt, O. Th., Traute, A., and Schmadl, H. Chem. Ber. (1960) 93, 556.
16. Boock, K., and Hall, L. D. Carbohydrate Res. (1975) 40, C3.
17. Dorman, D. E., and Roberts, J. D. J. Amer. Chem. Soc. (1970) 92, 1356.
18. deWit, G., Kieboom, A. P. G., and van Bekkum, H. Tetrahedron Lett. (1975) 45, 3943.
19. Scheurer, P. G., and Smith, F. J. Amer. Chem. Soc. (1954) 76, 3224.
20. Nishikawa, Y., Yoshimoto, K., Kurono, G., and Michishita, K. Chem. Pharm. Bull. (1975) 23, 597.
21. Isbell, H. S. Bur. Stand. J. Res. (1930) 5, 1179.
22. Robert, D., Tabone, J. Bull. Chim. Soc. France (1953) 206.
23. Fletcher, H. G., Jr. In "Methods in Carbohydrate Chemistry" II, 307, Academic Press, New York, 1963.
24. Jeanloz, R. W. In "Methods in Carbohydrate Chemistry" I, 214, Academic Press, New York, 1962.
25. Kaiser, C., Hillges, B., and Becker, F. Liebigs Ann. Chem. (1969) 725, 196.